EDITORIAL 10.1111/j.1469-0691.2009.02749.x

Is there a treatment for sepsis other than antibiotics?

M. Paul
Guest Editor
E-mail: pil1pel@zahav.net.il

Bacterial sepsis is a complex cascade of events that I cannot claim to begin to understand. Clearly, bacteria are involved, and they have many different toxic mechanisms, including the production of endotoxins, exotoxins, cytotoxins, and procoagulants. The host responds at the local and systemic levels with changes in gene regulation, recruitment of white blood cells, changes in the coagulation cascade, modification of signalling pathways, production of cytotoxins, and probably much more. Haemodynamic and metabolic changes result in, and affect, end-organ function. However, regardless of the pathways, in the current theme section we ask how we can treat sepsis. Early appropriate antibiotic treatment and haemodynamic resuscitation are indisputably the most important components of treatment. In this theme section, we go beyond the basics of current treatment to explore other modalities.

Cohen convincingly explains why antibiotics are not enough. He presents steps in the sepsis cascade where we should perhaps intervene, and the various modalities that have been designed for this. As theory is much more extensive than the drugs we currently have in our armamentarium for the treatment of sepsis, the question that arises is: does the probem lie in finding the right drug or knowing how to test it?

Minneci *et al*. present an updated systematic review and meta-analysis concerning the effects of corticosteroids on survival in sepsis. Their compilation of all trials to date and their analysis of these leads to some understanding of what underlies the effect of steroids in sepsis. They demonstrate that corticosteroids, started at *c.* 300 mg/day of hydrocortisone equivalents and reduced stepwise over *c.* 6 days, significantly improves overall survival. This effect was seen in severe sepsis, when mortality in the control group was above 25%, which corresponds to an APACHE II score of above 16.

Kopterides and Falagas summarize studies that have assessed statins in the context of sepsis. Statins represent but one of several non-antibiotic medications that have been claimed to improve survival in cases of sepsis. These claims originate from observational studies that, as Leibovici describes, examine chance findings and are prone to 'healthy user' bias. Although our ability to adjust for the healthy user bias when comparing patients treated or untreated with a chronic medication is *a priori* questionable, the studies assessing statins were particularly plagued by poor methodology and adjustment methods. It is therefore of some surprise that randomized controlled trials assessing statins for the treatment of sepsis are currently ongoing.

Houston and Cuthbertson present the evidence and controversies surrounding the use of activated protein C for the treatment of sepsis. Thirty-five years after the discovery of the molecule and after more than 10 years of clinical trials, we remain in a position with more questions than answers. An answer with some certainty exists only for the question of who should not be given activated protein C.

We did not review the topics of glucose control and nutrition in sepsis, which are of great relevance and are open to debate in the management of sepsis. We did not review many specific immune modulators that have been assessed in clinical trials. Ultimately, we can summarize that we have little to offer patients with severe sepsis other than adequate antibiotics and full haemodynamic support. A better understanding of the full implications of the sepsis cascade might yet yield more effective and individualized interventions.